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Need to bleed? Clozapine haematological monitoring approaches a time for change.

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Abstract:

Regular haematological monitoring during clozapine treatment reduces the risk of complications and death from clozapine-related blood dyscrasias. However, many patients in the course of clozapine treatment develop neutropenia unrelated to drug treatment but which leads to treatment discontinuation. The minimum haematological threshold allowed for continuation of clozapine treatment was recently lowered in the US, but not in the UK. In this case series, we present four cases where lowering the haematological cut-off to that used in the US, allowed treatment continuation. Lowering the current UK threshold for clozapine cessation could avoid unnecessary interruptions in treatment with minimal impact on safety.

Introduction:

Haematological monitoring during clozapine treatment is mandated to reduce the risk of clozapine-induced neutropenia and agranulocytosis. The cut-off point for clozapine cessation is somewhat arbitrary in that the evidence base that underpins the threshold is weak and there are worldwide variations in haematological monitoring parameters. Chance findings of apparent neutropenia during clozapine treatment that is probably unrelated to drug

treatment occurs frequently, usually leading to clozapine discontinuation. This in turn can lead to increased morbidity and prolonged hospitalisations and be detrimental to the quality of life of patients and their families. A single false result may also preclude use of clozapine for life. Given the increasing evidence that clozapine treatment is associated with reduced overall mortality (Wimberley et al 2017, Cho et al 2018), discontinuing clozapine in a patient with a marginal neutrophil count may not be in their long term interests.

Ethnicity is a major determinant of an individual's haematological profile, with neutrophil counts being substantially lower in people of African descent (Hsieh *et al.,* 2007). Frequent, repeated and often unnecessary requests for blood tests accounts at least in part for the underutilisation of clozapine in these patients (Whiskey *et al*., 2011). The use of separate haematological reference values for black and white patients had been long argued and so the introduction of monitoring according to Benign Ethnic Neutropenia (BEN) guidelines in the United Kingdom was a welcome development. This opened the way for patients that had hitherto been ineligible for this uniquely effective treatment.

The United States Food and Drugs Administration (FDA) introduced new clozapine monitoring guidelines in 2015. These guidelines give a lower Absolute Neutrophil Counts (ANC) cut-off for clozapine discontinuation (in both the general population and patients diagnosed with BEN) than in Europe. In addition, the requirement for monitoring total white blood cells (WBC) and platelets has been removed. It is expected that these changes will lead to many more patients in the United States being initiated and maintained on clozapine (Bastiampillai *et al.,* 2016).

The question that arises is – are the new US guidelines as safe as non-US guidelines, and if they are, why have they not been adopted around the world?

	Current UK Guidelines		Current US Guidelines	
Status	**General population criteria**	**BEN criteria**	**General population criteria**	**BEN criteria**
Green* WBC Neutrophils	 ≥ $3.5x10^9$/l ≥ $2.0x10^9$/l	 ≥ $3.0x10^9$/l ≥ $1.5x10^9$/l	 Not mandatory ≥ $1.5x10^9$/l	 Not mandatory ≥ $1.0x10^9$/l
Amber* WBC Neutrophils	 ≥ 3.0 and < $3.5x10^9$/l ≥ 1.5 and < $2.0x10^9$/l	 ≥2.5 and < $3.0x10^9$/l ≥ 1.0 and < $1.5x10^9$/l	 Not mandatory ≥ 1.0 and < $1.5x10^9$/l	 Not mandatory ≥ 0.5 and < $1.0x10^9$/l
Red* WBC Neutrophils	 < $3.0x10^9$/l < $1.5x10^9$/l	 < $2.5x10^9$/l < $1.0x10^9$/l	 Not mandatory < $1.0x10^9$/l	 Not mandatory < $0.5x10^9$/l

*Green – Continue treatment

*Amber – increase monitoring frequency

*Red – Discontinue treatment

In the following cases, adoption of the US Absolute Neutrophil Count (ANC) cut-off criteria enabled clozapine successful rechallenge.

Case 1:

Mr A is a 50-year old white British gentleman with a diagnosis of schizoaffective disorder. His first contact with psychiatric services was at around age 17 years. After various antipsychotic treatments, he started clozapine in 2000, which seemed to stabilise him very well over the years. In 2016 he was receiving clozapine 525 mg daily, amisulpride 200 mg BD and aripiprazole 5 mg daily. Over the 16-year period Mr A was on clozapine, he recorded several amber results that did not necessitate clozapine discontinuation. However in August 2016, he had a first red result with a neutrophil count of $1.25x10^9$/l and a white cell count of $2.30x10^9$/l which led to clozapine cessation. This period of neutropenia persisted over a two-week period where neutrophil counts ranged from 1.05 to $1.85x10^9$/l and WBC from 1.90 to $3.00x10^9$/l. There was no discernible medical explanation for the neutropenia. Upon discontinuation of clozapine, the patient suffered a significant deterioration in mental state requiring admission to a psychiatric intensive care unit. Treatment with high dose and combination antipsychotics did not alleviate his psychotic symptoms. Treatment with two courses of Electroconvulsive Therapy (ECT), each of 12 sessions, brought about a degree of improvement which was not sustained. Mr A remained thought-disordered and incoherent and was on a 2:1 nursing observation upon admission to our unit in November 2017. On admission, he was prescribed

olanzapine 30mg daily and lithium 800mg daily. His neutrophil count on admission was $2.7x10^9$/l and WBC $4.2x10^9$/l. All other investigations were within normal limits apart from a slightly elevated fasting blood sugar.

After haematology consultation, a care plan for clozapine rechallenge was developed and he was restarted. Within a few weeks, his mental state started to show significant improvement. However, within 3 months of restarting clozapine, he had recorded six amber results using the general population criteria, requiring multiple and frequent blood tests with neutrophil counts ranging from 1.6 to $1.9x10^9$/l and WBC from 3.0 to $3.5x10^9$/l. This prompted the team to refer for another haematology consultation and agreement was reached with the clozapine registry to use revised monitoring protocols in line with US criteria. At 6 months follow-up, there have been no further amber or red results on the new criteria and the patient continues to make progress on clozapine treatment without the need for frequent and repeated blood testing.

Case 2:

Mr B is a 49-year old white British male with a diagnosis of treatment-resistant schizoaffective disorder who was started on clozapine in 2003 and for the most part was treated with clozapine, sodium valproate and various antidepressants until 2015 when he stopped and refused to restart clozapine. Although he had responded well to clozapine treatment and was living in the community during this period, he complained of a variety of side effects such as sedation and weight gain. After clozapine cessation, he was treated with numerous oral and long-acting antipsychotic drugs such as zuclopenthixol decanoate and olanzapine at

maximum licensed doses but without response. Eventually, he was referred to our unit for a clozapine retrial. On admission to our unit in March 2017, his prescribed medications were zuclopenthixol decanoate 500mg weekly and sodium valproate 500mg daily. The blood picture showed WBC $3.6x10^9$/l, neutrophils $1.8x10^9$/l and platelets $131x10^9$/l. All other blood results were normal. In view of the plan to start clozapine, and our previously published evidence that sodium valproate treatment is associated with an increased risk of neutropenia in clozapine-treated patients (Meyer *et al*., 2015; Malik *et al*., 2018), sodium valproate was gradually discontinued. However, the patient refused to accept lithium, which we use to provide mood stabilisation but which also has the capacity to boost neutrophil counts (Whiskey and Taylor, 2007). Before clozapine initiation, the haematological picture had improved and WBC was $4.85x10^9$/l, neutrophils $2.47x10^9$/l and platelets $159x10^9$/l. Clozapine was eventually commenced in May 2017 and the dose gradually increased. This was followed by significant improvement in mental state. Over the next 10 months, using general UK population criteria, there were four amber results and one red result. Consequently, in March 2018 we consulted with haematology specialists regarding lowering the monitoring parameters in accordance with the US protocol which was agreed and adopted by the clozapine registry. At 14 months follow up, the patient continued clozapine monotherapy without the need for discontinuation owing to low neutrophil counts using the modified criteria.

Case 3

Ms C is a 46-year old white British female with a diagnosis of treatment-refractory schizophrenia. She was diagnosed with schizophrenia in 1996 at age 24. She was commenced on clozapine treatment in June 2000 to which she demonstrated a response, but after 3 months on treatment, it was discontinued after two red results with a nadir of neutrophils at $1.7x10^9$/l and WBC of $2.85x10^9$/l. Over the next 17 years, she was tried on a variety of first and second generation antipsychotic drugs without much improvement. Although clozapine was contemplated on a few occasions its use was not attempted until she was referred to our unit in 2017. On admission in November 2017, her prescribed medications were zuclopenthixol decanoate 500mg 2-weekly and the antidepressant agomelatine. Her psychotic symptoms were prominent and encompassed most aspects of her life. The main delusional themes revolved around passivity in religious, mythological and sexual ideas (first rank Schneiderian experiences), in addition to delusions of grandeur and persecution. There were also auditory, visual and somatic hallucinations, which had been effectively untreated for many years. Her haematological profile on admission was normal with a WBC of $4.5x10^9$/l, neutrophils of $3.5x10^9$/l and a platelet count of $221x10^9$/l. She had a slightly raised HBA1c of 6.3% (on metformin). All other biochemical tests were normal. We sought haematology advice and the patient was able to commence clozapine in February 2018. However, within one month of clozapine initiation, an amber result was recorded with a WBC of $3.3x10^9$/l (neutrophils were normal at $2.4x10^9$/l). To reduce the risk of clozapine discontinuation, we sought another haematology review to allow revised monitoring according to the US criteria which was agreed. The patient has been on this treatment plan for the last 6 months without any amber or red results (according to US criteria) with substantial improvement in her psychotic symptoms.

Case 4:

Ms D is a 49-year old Chinese female with treatment-resistant schizophrenia and multiple medical co-morbidities. Her medical history includes Systemic Lupus Erythematosus (not active), and Autoimmune Haemolytic Anaemia (related to the SLE) – both stable on low dose steroids. She also had Chronic Kidney Disease stage 3 and had had deranged Liver Function Tests (LFT) for many years. Her MRI showed white matter hyperintensities and tonic-clonic seizures had been reported in June 2015. She had frequent low magnesium levels and was intermittently prescribed supplements. She also had a history of type 2 diabetes, hypertension, hypercholesterolemia and recurrent Urinary Tract Infections (UTIs). Her very complicated medical picture together with a chronically low WBC had precluded a clozapine trial for over two decades until she was referred to our unit in December 2016. After extensive medical reviews by various specialists, clozapine was initiated in May 2017. Baseline investigations showed a WBC of $3.7x10^9$/l and neutrophils of $2.26x10^9$/l. Within 8 weeks of clozapine initiation, there was a remarkable improvement in her mental state and presentation. However during the same period, there were three amber results (using UK general population criteria) resulting in the requirement for twice weekly blood monitoring. We therefore undertook another haematology consultation to allow revised monitoring according to the US criteria, which was agreed with the clozapine registry. Despite monitoring according to the revised criteria, clozapine was discontinued in November 2017 and restarted after 10 days following two red results (WBC $2.05x10^9$/l and neutrophils $1.2x10^9$/l; WBC $2.2x10^9$/l and neutrophils $1.3x10^9$/l). In this instance, clozapine treatment was interrupted

owing to the low total white cell count and not because of the neutrophil count. Eight months later, the patient has continued clozapine and maintains improvement in her mental state

Discussion

The role of clozapine in the treatment of patients with refractory psychotic illness is undisputed and it is not an exaggeration to say that its reintroduction in the 1990s radically changed many lives. However, it is also associated with a risk of some rare but potentially life-threatening adverse reactions such as neutropenia, agranulocytosis, myocarditis and severe constipation. A significant proportion of patients are referred to the National Psychosis Unit (NPU), a tertiary-care clinical-academic psychiatric facility in South London, for possible clozapine rechallenge following the occurrence of some of these potentially serious adverse effects. The unit works in close collaboration with various medical specialties and thus patients undergo thorough medical evaluations before such a rechallenge is undertaken.

The cumulative incidence of agranulocytosis during clozapine treatment is estimated at 0.8% (Alvir *et al*., 1993) and that of neutropenia to be about 3% (Atkin *et al*., 1996). To mitigate these risks, various guidelines have been adopted in different countries. Regular blood monitoring is mandatory in most countries. However, not only is there wide variation in the frequency of blood monitoring across different countries, but the haematological threshold for clozapine treatment cessation also differs (Nielsen *et al*., 2016). This variation is not surprising as the evidence base for the details of haematological monitoring frequency and thresholds for cessation is weak and inevitably somewhat arbitrary.

In Iceland, haematological monitoring during clozapine treatment is flexible and not rigorously enforced. In a study of patients with schizophrenia comparing those on long-term clozapine treatment versus non-clozapine antipsychotics, mild neutropenia (1.5-1.9 $x10^9$/l) was significantly associated with clozapine compared with non-clozapine drugs (hazard ratio of 1.86). Moderate to severe neutropenia (0-1.4 $x10^9$/l) on the other hand was more common in patients who had never been on clozapine despite having blood counts half as frequently as those on clozapine (Ingimarsson *et al*., 2016). The Iceland data suggest that many instances of neutropenia are probably unrelated to clozapine and very rarely progress to the more severe agranulocytosis. The authors, Ingimarsson et al, call for a lower limit in line with the current US guidelines. This is also consistent with reports that transient neutropenia occurs frequently during clozapine treatment (Hummer *et al*., 1994).

Studies examining clozapine rechallenge in patients who developed neutropenia during treatment demonstrate that greater than 70% of challenges are successful (Meyer *et al*., 2015; Prokopez *et al*., 2016). This suggests that many cases of neutropenia during clozapine may be chance findings, and that different mechanisms underlie the more benign neutropenia and the potentially lethal agranulocytosis. This further lends support to the results from the Icelandic study suggesting the risk of severe neutropenia or agranulocytosis with clozapine is probably not significantly different from other antipsychotic agents.

It is well recognised that among the known barriers contributing to gross world-wide underutilisation of clozapine is the requirement for blood monitoring (Gee *et al*., 2014; Farooq *et al*., 2018). In a survey of international trends in clozapine use, Japan recorded the

lowest clozapine use which can be partially explained by the very strict regulations around clozapine initiation, including weekly haematological tests for 26 weeks and hospitalisation for the first 18 weeks (Bachmann *et al.,* 2017).

Two strategies commonly employed to manage clozapine-associated neutropenia are the use of lithium (Paton and Esop, 2005) and Granulocyte Colony-Stimulating Factor (G-CSF) (Lally *et al*., 2017; Myles *et al*., 2017). These strategies are not without risks. The combined use clozapine and lithium may increase the risk of neurotoxic reactions (Bender *et al*., 2004) while there is a paucity of data on the use of G-CSF in preventing clozapine-associated haematological adverse effects (Lally *et al.,* 2017). Long-term G-CSF adverse effects can include enlarged spleen, hepatomegaly, urinary abnormalities and very rarely, splenic rupture (Khan *et al*., 2013). It could be argued that with the lowering of the threshold using the US criteria, such remedial strategies could become unnecessary in most instances.

In two of the cases, (patients C and D), clozapine was discontinued not because of the neutrophil counts but because of the total white cell count (WCC). The need for clozapine cessation would have been unnecessary under the new US guidelines where the threshold for WCC has been removed. An evaluation of the Clozapine Monitoring Programme for 1100 patients registered for treatment at the South London and Maudsley NHS Foundation Trust from January to December 2017 showed 18 patients recorded 57 “red” results during the period. Of these, 16 results (from 6 patients) were due to a low total white cell count rather than low absolute neutrophil counts. At follow up in 2018, three of these patients have ceased clozapine treatment while three have continued.

The impact and clinical safety of the new US guidelines have not been fully assessed. An analysis of the potential impact of the changes using the Veterans Integrated Service Network 7 (VISN 7) involving 246 clozapine recipients from 1999 to 2012 has been conducted (Sultan *et al*., 2017). Under the old regulations, 5 patients (3.1%) of 160 qualified for clozapine cessation, whereas under the new guidelines, only 1 (0.6%) qualified for treatment discontinuation.

Conclusion:

Clozapine is currently the most effective treatment available for patients with refractory schizophrenia but it is grossly underutilised. Mandatory haematological monitoring is a double-edged sword. On one hand, it reduces clozapine-associated haematological toxicity; but on the other hand it precludes its use among patients who experience transient neutropenias that are probably unrelated to drug treatment. Adoption of BEN monitoring guidelines was a positive step in the right direction that has allowed may black patients to access clozapine treatment. It is timely to consider adopting the US guidelines. This would obviate the need for frequent, repeated blood testing and unnecessary termination of treatment. In addition, it would further increase the potential number of patients that would benefit from this uniquely effective but underused treatment without compromising safety.

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